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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,319	08/19/2003	Michael D. Ruff	019031-000010	3826

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WOMBLE CARLYLE SANDRIDGE & RICE, PLLC  
ATTN: PATENT DOCKETING 32ND FLOOR  
P.O. BOX 7037  
ATLANTA, GA 30357-0037

EXAMINER

OH, SIMON J

ART UNIT	PAPER NUMBER
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1618

MAIL DATE	DELIVERY MODE
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12/20/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/643,319	<b>Applicant(s)</b> RUFF ET AL.	
	<b>Examiner</b> Simon J. Oh	<b>Art Unit</b> 1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 29 October 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 42-46, 49-53 and 55-57 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 42-46, 49-53 and 55-57 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Papers Received***

Receipt is acknowledged of the applicant's amendment, response, and request for continued examination, all received on 29 October 2007. Receipt is acknowledged of the applicant's change in power of attorney, received on 06 September 2007.

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 29 October 2007 has been entered.

### ***Claim Rejections - 35 USC § 112***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The rejection of Claims 43-46, 49-53 and 56 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of the present amendment to Claim 43.

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The rejection of Claims 43-46, 49-53 and 55 under 35 U.S.C. 103(a) as being unpatentable over Busetti *et al.* (U.S. Patent No. 5,788,987) in view of Norling *et al.* (U.S. Patent No. 5,958,458) is hereby withdrawn.

The rejection of Claims 56 and 57 under 35 U.S.C. 103(a) over Busetti *et al.* (U.S. Patent No. 5,788,987) in view of Norling *et al.* (U.S. Patent No. 5,958,458) and Ekwuribe *et al.* (U.S. Patent Application Publication No. 2003/0050228) is hereby withdrawn.

Claims 43-46, 49-53 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Norling *et al.* (U.S. Patent No. 5,958,458) in view of Busetti *et al.* (U.S. Patent No. 5,788,987).

The Norling *et al.* patent teaches a pharmaceutical multiple unit formulation in the form of coated cores. The core material is selected from various materials that include calcium carbonate, calcium silicate, calcium magnesium silicate, calcium phosphate, and kaolin (See Abstract). Various substances may be applied as coatings to the cores, including waxes, hydrogenated oils, and glyceryl monostearate. The coating material may be admixed with excipients that include colloidal silicon dioxide, talc, and magnesium stearate. The coating material may further comprise plasticizers, such as castor oil, mineral oil, and coconut oil (See Column 9, Line 41 to Column 10, Line 57). Film coatings comprising polymers such as ethylcellulose may be included in the disclosed composition (See Column 9, Lines 43-50). The

disclosed composition may be embodied in various formulations, including powders, granules, tablets, as well as liquid formulations (See Column 13, Lines 29-36). The cores may also comprise an active substance, which may be coated onto the surface of the cores (See Column 11, Lines 57-67). The active substance may be selected from various broad categories of agents, including insulin (See Column 7, Lines 60-67). The patent discloses examples where inert cores are prepared and where varying amounts of various coating materials are applied to these cores (See Example 1A to Example 10). A recited feature of the disclosed invention is its control of particle size for the purpose of increasing the likelihood of patient compliance.

The Norling *et al.* patent does not teach the specific use of dibasic calcium phosphate dihydrate as a core excipient.

The Buseti *et al.* patent teaches controlled release dosage forms comprising a core containing the active agent and coated with a polymeric layer (See Abstract). Suitable active agents include peptide drugs such as insulin (See Column 4, Lines 33-38). Suitable materials for use in the core include dibasic calcium phosphate dihydrate (See Column 4, Lines 39-50). The dosage forms may be pressed into tablets or used to fill capsules (See Column 5, Lines 19-24).

It is the position of the examiner that the instantly claimed invention is made obvious by the disclosure of the prior art. As the prior art references are both drawn to dosage forms having a coated core, they are considered to be analogous. One of ordinary skill in the art would have the required knowledge and skill to substitute the dibasic calcium phosphate dihydrate as disclosed in Buseti *et al.* into the dosage form disclosed by Norling *et al.*, which already discloses calcium phosphate as a core excipient. The substitution of calcium phosphate with a more specific form in dibasic calcium phosphate dihydrate is a change that can be accomplished

by one of ordinary skill in the art with a reasonable expectation of success. Furthermore, the prior art disclosure of the core material being coated with various excipients such as hydrogenated oils and magnesium stearate, it is the position of the examiner that this disclosure reads on what the applicant was chosen to define as a permeation enhancer. Thus, the instantly claimed invention is *prima facie* obvious.

Claims 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Norling *et al.* (U.S. Patent No. 5,958,458) in view of Buseti *et al.* (U.S. Patent No. 5,788,987) and Ekwuribe *et al.* (U.S. Patent Application Publication No. 2003/0050228)

The Norling *et al.* patent teaches a pharmaceutical multiple unit formulation in the form of coated cores. The core material is selected from various materials that include calcium carbonate, calcium silicate, calcium magnesium silicate, calcium phosphate, and kaolin (See Abstract). Various substances may be applied as coatings to the cores, including waxes, hydrogenated oils, and glyceryl monostearate. The coating material may be admixed with excipients that include colloidal silicon dioxide, talc, and magnesium stearate. The coating material may further comprise plasticizers, such as castor oil, mineral oil, and coconut oil (See Column 9, Line 41 to Column 10, Line 57). Film coatings comprising polymers such as ethylcellulose may be included in the disclosed composition (See Column 9, Lines 43-50). The disclosed composition may be embodied in various formulations, including powders, granules, tablets, as well as liquid formulations (See Column 13, Lines 29-36). The cores may also comprise an active substance, which may be coated onto the surface of the cores (See Column 11, Lines 57-67). The active substance may be selected from various broad categories of agents,

including insulin (See Column 7, Lines 60-67). The patent discloses examples where inert cores are prepared and where varying amounts of various coating materials are applied to these cores (See Example 1A to Example 10). A recited feature of the disclosed invention is its control of particle size for the purpose of increasing the likelihood of patient compliance.

The Norling *et al.* patent does not teach the specific use of dibasic calcium phosphate dihydrate as a core excipient, nor does it teach hexyl insulin monoconjugate-2 polydisperse.

The Buseti *et al.* patent teaches controlled release dosage forms comprising a core containing the active agent and coated with a polymeric layer (See Abstract). Suitable active agents include peptide drugs such as insulin (See Column 4, Lines 33-38). Suitable materials for use in the core include dibasic calcium phosphate dihydrate (See Column 4, Lines 39-50). The dosage forms may be pressed into tablets or used to fill capsules (See Column 5, Lines 19-24).

The Ekwuribe *et al.* reference discloses methods for the treatment of diabetes where oral compositions of insulin drugs are administered, for the purpose of administering insulin to a subject in need thereof through routes that are more convenient than the traditional method of subcutaneous administration of insulin (See Claim 1; and Sections 0003 to 0017). To this end, the Ekwuribe *et al.* reference discloses insulin polypeptides that are suitable for oral administration, such as HIM2 (See Sections 0133 to 0134). Solid pharmaceutical formulations for oral administration such as powders and granules are disclosed (See Section 0145).

It is the position of the examiner that the instantly claimed invention is made obvious by the disclosure of the prior art. As the prior art references are both drawn to dosage forms having a coated core, they are considered to be analogous. One of ordinary skill in the art would have the required knowledge and skill to substitute the dibasic calcium phosphate dihydrate as

disclosed in Buseti *et al.* into the dosage form disclosed by Norling *et al.*, which already discloses calcium phosphate as a core excipient. The substitution of calcium phosphate with a more specific form in dibasic calcium phosphate dihydrate is a change that can be accomplished by one of ordinary skill in the art with a reasonable expectation of success. Furthermore, the prior art disclosure of the core material being coated with various excipients such as hydrogenated oils and magnesium stearate, it is the position of the examiner that this disclosure reads on what the applicant was chosen to define as a permeation enhancer.

Furthermore, one of ordinary skill in the art would have the requisite skill to substitute the insulin disclosed in Norling *et al.* with the insulin polypeptides disclosed in the Ekwuribe *et al.* reference. One of ordinary skill in the art would be motivated to make such a substitution as such insulin drugs are disclosed as being better suited for the oral administration of insulin. As both prior art references are drawn to oral pharmaceutical formulations that contain an insulin drug, they are considered analogous to one another and one of ordinary skill in the art would therefore have a reasonable expectation of success in making the aforementioned substitution to arrive at the instantly claimed invention. Thus, the instantly claimed invention is *prima facie* obvious.

#### ***Response to Arguments***

Applicant's arguments with respect to claims 42-46, 49-53 and 55-57 have been considered but are moot in view of the new ground(s) of rejection.

*Correspondence*

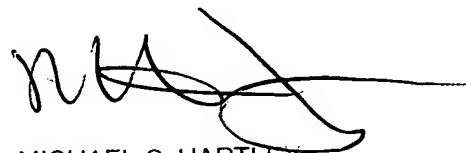
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Simon J. Oh whose telephone number is (571) 272-0599. The examiner can normally be reached on M-F 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Simon J. Oh  
Examiner  
Art Unit 1618

sj0

A handwritten signature in black ink, appearing to read 'Michael G. Hartley', with a long horizontal stroke extending to the right.

MICHAEL G. HARTLEY  
SUPERVISORY PATENT EXAMINER